

VIP: MOLECULAR GENETICS AND CHEMICALLY DESIGNED ANALOGUES. Illana Gozes, Dept. Pathological Chemistry, Tel Aviv Univ. Faculty of Med., Tel Aviv 69978 Israel.

Vasoactive intestinal peptide (VIP) is a major neuropeptide exhibiting in vitro roles in neurotrophism, growth promotion, neurotransmission and regulation of energy metabolism. Additionally, exogenous VIP has been shown to stimulate sexual behavior. To address the question of the involvement of VIP in complex behaviors two independent complementary approaches were taken.

In one approach, transgenic mice harboring a chimeric VIP gene driven by the polyoma promoter were produced. Successful incorporation of the foreign gene was ascertained by DNA restriction mapping using the polyoma promoter as a hybridization probe. RNA blot analysis showed two transgenic specific, VIP-related RNA species. Behavioral studies revealed learning impairment and prolonged retardation in memory acquisition in the transgenic animals as evaluated in the Morris swim maze. Furthermore, reduced performance was observed when the male transgenic mice were tested for sexual activity in the presence of receptive females. Surprisingly radioimmunoassays showed a small decrease in the VIP content in the transgenic mice brains. To directly assess genetically reduced VIP content as a cause for learning impairment, transgenic mice carrying diphtheria toxin encoding sequences driven by the VIP promoter were developed. These animals had reduced brain VIP and exhibited deficiencies in learning abilities, strongly supporting an important neurobiological function for VIP in vivo.

In the second approach to assess VIP biological function in vivo and in vitro we have developed novel VIP antagonists e.g. a VIP-neurotensin hybrid antagonist which can differentiate between central and peripheral VIP receptors. This antagonist can induce neuronal cell death in vitro and inhibit the acquisition of milestones in the development of behavioral reflexes when chronically injected to developing rats. When administered intracerebrally to adult animals this antagonist causes impairment of learning and memory acquisition. The structural/functional aspects of VIP activity in the nervous system are now being elucidated using a family of agonists and antagonists. The mechanism by which the VIP-antagonist induced neuronal cell death may be mediated via novel growth factors associated with VIP.